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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
LUCAS, ZACHARIAH

ART UNIT	PAPER NUMBER
1648	10

DATE MAILED: 09/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/367,052	Applicant(s) KISHIMOTO ET AL.	
	Examiner Zachariah Lucas	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *6-9, 14, 15, 17-21, and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 10-12, 16, 22* is/are rejected.

7)☒ Claim(s) *13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5-7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Claims 6-9, 14, 15, 17-21, and 23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

2. Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the Examiner is required to rejoin the claims to the DNA and the protein encoded thereby under PCT Rule 13.1 as illustrated by Example 17 of the PCT Administrative Instructions. This is not found persuasive for several reasons. First, while the PCT Administrative Instructions are useful in making determinations as to the presence of Unit of Invention among inventions, the Examples are merely guides, and are not binding.

Second, the U.S. has set forth specific categories in 37 CFR 1.475 where Unity of Invention will be found. Claims to two different products, as is the case with nucleic acid and amino acid sequences, are not among these classes of inventions where Unity of Invention will be found.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on August 6, 1999, February 6, 2003, and March 11, 2003 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Specification

4. The disclosure is objected to because of the following informalities: on page 15, lines 17-19, the specification in describing Figure 1, indicates that the figure discloses an "amino acid sequence ... encoding the above nucleic acid sequence." It is suggested that the specification be amended to clarify that the amino acid sequence is "encoded by" the nucleic acid sequence.

Appropriate correction is required.

5. The disclosure is objected to because of the following informalities: in many instances where the application refers to a sequence identifier, the application identifies the sequences as "of Sequence Listing." It is requested that in each such instance, the specification be amended such that either the article -- the-- is inserted in front of the term "Sequence listing," or that the phrase "of Sequence Listing" is deleted.

Appropriate correction is required.

Claim Objections

6. Claims 1-4 are objected to because of the following informalities: each of these claims, when referring to a SEQ ID NO:, continues, after identifying the sequence number, "of Sequence listing." It us suggested that the claims be amended such that either the article --the-- is inserted in front of the term "Sequence listing," or that the phrase "of Sequence Listing" is deleted.

Appropriate correction is required.

7. Claim 13 is objected to because of the following informalities: This claim reads on a method of producing a polypeptide by culturing a cell "under condition capable of expressing the expression vector according to claims 10." It is suggested that the claim be amended such that it reads on a method wherein the cell are cultured "under conditions wherein the transformant is capable of expressing the expression vector..."

Appropriate correction is required.

8. Claim 13 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). This claim depends from claims 11 and 12 in the alternative, and from claim 10. Accordingly, the claim has not been further treated on the merits.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-5, 10-12, 16, and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims read on DNAs (and compositions thereof) encoding "an entire sequence of the amino acid sequence as shown by SEQ ID NO: 2..." or comprising "an entire sequence of the nucleotide sequence as shown by SEQ ID NO: 1..." These claims are rejected because it is unclear what is meant by the phase "an entire sequence of the [amino acid/nucleotide] sequence..." It is unclear whether the Applicant intends that the phrase limit the described embodiment to the sequence of SEQ ID NO: 2 or SEQ ID NO: 1 (respectively), or if the phrase includes any sequence within (fragments of) the identified sequences. Clarification is required.

11. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim reads on DNAs capable of hybridizing to SEQ ID NO: 1 under stringent conditions. However, the Applicant has not identified what is meant by the term "stringent." Because this is a relative term, and because the scope of DNAs that fall within the claim depends on what is meant by the term "stringent" the claim is indefinite.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-5, 10-12, 16, and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims read on a genus of inventions comprising the nucleic acid of SEQ ID NO: 1, or fragments or derivatives (DNAs with a substitution, deletion, insertion, or addition in comparison to the sequence of SEQ ID NO: 1) thereof encoding a polypeptide capable of binding to PBSF/SDF-1.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

In the present case, while the Applicant has disclosed SEQ ID NO: 1, and nucleic acids encoding fragments thereto, the Applicant has not disclosed fragments that bind to the identified

ligands (or identified the disclosed fragments as so capable). Because the Applicant has not identified any fragments or derivatives of SEQ ID NO: 1 that are capable of binding to the identified ligands, and because the Applicant has not identified the region or residues of SEQ ID NO: 1 that are capable of binding to these ligands, the Applicant has not provided an adequate description by which one skilled in the art could identify the claimed genus of inventions. Thus, the Applicant has not met the written description requirements of 35 U.S.C. 112 ¶ 1.

14. Claims 1-5, 10-12, 16, and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising the full sequence of SEQ ID NO: 1, does not reasonably provide enablement for embodiments comprising only fragments of or comprising derivatives of the sequence that encode polypeptide capable of binding to murine PBSF/SDF-1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims have been described above. As was also indicated above, while the Applicant has disclosed the full length coding and protein sequences of the murine CXCR4, the Applicant has not shown what portions of the murine receptor are necessary for binding, or what residues are necessary for the receptor to bind to PBSF/SDF-1. Thus, while the claims cover a broad scope of inventions, the specification provides only a single working example, and little or no guidance as to what portions or residues of the polypeptide (thus the DNA) sequence are open to modification without a loss of activity.

However, it is known in the art that, while proteins are generally open to modification, the effects of any particular modification to the protein's function cannot be predicted from the sequence alone. See e.g. Bowie et al., Science 247: 1306-1310 (esp. page 1306, first full paragraph in right column). In the present case, the Applicant has not indicated what residues of the disclosed protein would tolerate modification. While the Applicant has indicated that the protein shares significant homology to the human CXCR-4 receptor, the Applicant has not demonstrated that the binding domains of the two receptors share a common motif or that the ligands to these receptors share common structures and bind to like regions of the receptors. Further, the art also teaches that, while the human and murine CXCR-4 receptors are overall about 90% homologous, the majority of the differences between the two proteins may be found in the extracellular regions, which share only 74% homology. See, Heesen et al. (J Immunol 157: 5455-60- of record in the IDS filed on August 6, 1999), J. Immunol 157: 5455-60, at page 5457, last full paragraph. Thus, absent further data, one of ordinary skill in the art would not know what modifications to the protein would result in the loss of protein function, or what fragments of the protein would be capable of binding to the identified ligand.

In view of the limited guidance provided by the Applicant, the scope of the claims, and unpredictability of the art, the Applicant has not provided sufficient information to enable those in the art to make or use any derivative or portion of the identified CXCR-4 receptor. Thus, the Applicant is also not enabled for the claim polynucleotides encoding such fragments and derivatives.

15. Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim reads on a DNA capable of hybridizing under stringent conditions to a DNA encoding a polypeptide that binds to PBSF/SDF-1, and that simultaneously encodes for a polypeptide having the activity of binding to such a polypeptide. Because a first nucleic acid that hybridizes to a second nucleic acid does not encode the same polypeptide as the second nucleic acid, and because the Applicant has not shown that a polypeptide encoded by such a hybridization partner is capable of binding the identified ligand, the Applicant is not enabled for the hybridization partners with the identified activity.

16. Claim 22 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while potentially being enabling for a kit for the detection of HIV-1 infection comprising a cell transfected with a polynucleotide encoding CXCR-4 and CD4, does not reasonably provide enablement for a kit for the detection of the onset of AIDS, or for kits for detecting HIV infection wherein the cells express CD4, and only a portion of the CXCR-4 receptor that binds to murine PBSF/SDF-1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The claim is rejected on two grounds. First, the Applicant has not established that the claimed kit (or method of using it) would be capable of determining the onset

of AIDS. Second, the Applicant has not established that the kit could be used wherein cells of the kit do not comprise the full murine CXCR-4.

With regards to the first ground of rejection, the Applicant has not demonstrated that the claimed kit would be useful for detecting the onset of the AIDS disorder. The Applicant has indicated that the cells expressing the murine CXCR4 receptor can be bound by HIV-1, thereby allowing for the use of the cells to detect infection by the virus. However, the Applicant has not demonstrated that the cells can be used to distinguish between infection by the HIV-1 virus, and the onset of the AIDS disorder. Because the Applicant has not demonstrated that the kit may be used in such a method, or how to use the kit to determine the onset of AIDS, the Applicant is not enabled for the kit to the extent that it exceeds the detection on HIV-1 infection.

With regards to the second basis for rejection, the Applicant has not shown that any murine CXCR-4 derivative or fragment that is capable of binding to PBSF/SDF-1 would be capable of also binding to HIV. As indicated above, the Applicant has provided little guidance that would lead those in the art to derivatives or fragments of the murine receptor that could bind the identified ligand. In addition to this, the Applicant has not established either that HIV binds to CXCR-4 through the same mechanism/motif as used by the identified ligand, or that a receptor capable of binding the ligand is per se capable of being bound by HIV. Thus, for substantially the same reasons as indicated above with regards to the derivatives and fragments of the protein that can bind the ligand, the Applicant is also not enabled for derivates or fragments of the receptor that can be bound by HIV. Thus, the Applicant is also not enabled for kits for the detection of HIV that comprise murine CXCR-4 derivatives or fragments.

17. Claim 22 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for kits comprising the cell recombinantly expressing hCD4 and mCXCR-4, does not reasonably provide enablement for HIV detection kits comprising any cell that expresses human CD4 (hCD4) and murine CXCR-4 (mCXCR-4). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. As indicated above, the claim reads on kits for the detection of any HIV infection comprising a cell that expresses a murine CXCR-4 and a human CD4 receptor. Further, the Applicant has also demonstrated that, when these receptors are expressed in recombinant NIH3T3 and SW480 cells, these cells were capable of either fusing cells expressing HIV envelope proteins, or of being infected by HIV. App. pages 58-60. Thus, the Applicant has demonstrated that some cells recombinantly made to express murine CXCR-4 and human CD4 may be useful for the detection of infection by some strains of HIV. Thus, the claim is rejected on two grounds. First, the Applicant is not enabled for kits comprising any cell expressing hCD4 and mCXCR-4. Second, the Applicant is not enabled for a kit that can detect infection by any strain of HIV.

In contrast to the teachings of the application, the art indicates that not all cells expressing hCD4 and mCXCR-4. See e.g., Heesen et al. (J Immunol, supra). As indicated by this reference, and reaffirmed by the teachings of Bienasz et al. (J Virol 71(9): 7097-100), many cells expressing homogenous mCXCR-4 were not able to fuse with cells expressing HIV env proteins or were not permissive to HIV infection. However, Bieniasz also discloses, as does the present Applicant, that cells transfected to express the heterologous hCD4 and mCXCR-4 receptors were permissive to binding and infection by certain strains of HIV. Page 7097. Thus, the Applicant is

not enabled for any cells that express hCD4 and mCXCR-4, but is enabled for cells that express the receptors exogenously. Further, as both the art (Bieniasz, paragraph spanning pages 7097-98, and page 7099), and the application (pages 59-60, esp. page 60, lines 15-19), indicate that some viruses, but not others, are capable of binding and infecting cells with hCD4 and mCXCR-4. It is therefore suggested that the claim be amended to limit the kit to cells transfected with exogenous DNA to express the two receptors, and that the intended use language (in the claim preamble) be amended to read either on a kit, or a kit for detecting infection by the HIV strains NL432 or IIIb.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

19. Claims 1, 3, 10-12, and 16 are rejected under 35 U.S.C. 102(a) as being anticipated by Nagasawa et al., PNAS 93: 14725-29 (of record in the IDS of August 6, 1999). The reference discloses the isolation of DNA encoding for the murine CXCR-4 receptor, and the cloning and transfection of CHO cells therewith. See, pages 14726-28. Thus, the reference teaches the currently claimed invention.

20. Claims 16 and 22 are rejected under 35 U.S.C. 102(a) as being anticipated by either of Heesen et al. (supra), or Ashorn et al., J Virol 64: 2149-56. These claims read on a cell expressing the receptor encoded by the polynucleotide of claim 1, and a CD4 receptor. Each of

Heesen and Ashorn discloses a CD4 bearing A20 cell that also, according to Heesen, appears to express the CXCR-4 receptor. Heesen, pages 5457-58, and Ashorn, pages 2149, and 2151, and page 2153 Table 1. Further, the references disclose the use of these cells to determine HIV binding. While it is noted that the disclosed cells were not capable of binding to the virus, the cells themselves meet the limitations of the rejected claims. Thus, because the cells meet the structural limitations of the claims, the fact that the cells are apparently unsuitable for the intended sue of the claims is not sufficient to distinguish the claimed products from those disclosed in the references.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 1, 3, 10, 11, and 12 are rejected under 35 U.S.C. 103(a) as obvious over Heesen et al. (J Immunol, supra). These claims describe polynucleotides, and cells comprising and expressing them, that encode for the disclosed murine CXCR-4 receptor. Heesen also teaches the presence of this receptor on murine cells. Further, the reference also teaches the isolation of fragments of the DNA that encode the receptor, and the sequencing of the DNA therefrom. While the reference does not actually teach isolation of the claimed polynucleotide, it provides sufficient information that one of ordinary skill in the art would have been able to isolate the

DNA themselves. Having so described the receptor's coding DNA, the reference also renders obvious vectors comprising the DNA and cells transfected therewith.

Conclusion

23. No claims are allowed.

24. The following prior art reference is made of record and is considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> Lores et al, AIDs Res Hum Retroviruses, 8(12): 2063-71. This reference teaches that murine cells transfected with human CD$ were not found permissive to HIV infection. The reference also teaches on page 2069 that mouse cell "do not possess the adequate receptor and the putative accessory molecules for HIV binding and entry." Thus, the reference supports the teachings of Heesen and Bieniasz.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner

JAMES HOUSEL 9/22/03
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